Clinical Trials

Part 7

PUBLISING THE RESEARCH

1. Publication planning
2. Guidelines for reporting clinical trials
3. Principles for constructing good graphs and tables
4. Analysis of a published manuscript

PUBLICATION PLANNING

- Identify potential manuscripts at time of study design and include publication plan in protocol
  - primary manuscript
    - report main results of study
  - secondary manuscripts
    - study design paper and baseline patient characteristics
    - secondary objectives
    - substudies
  - tertiary manuscripts
  - arise after study is planned

AUTHORSHIP POLICY

- If not specified in advance, can be a very contentious issue at time of publication
- Who will be listed as an author?
- What order?
- What is the intended journal?
  - May have its own rules
  - number of authors
  - group authorship

AUTHORSHIP POLICY

- Current thinking
  - each author must have played a substantive role in the design of the study and/or the development of the manuscript
  - local investigators who recruit and follow patients, data collectors, etc. should not be credited unless they meet this qualification

WRITING/PUBLICATION COMMITTEE

- identifies potential manuscripts
- sets general authorship policy
- assigns one or more people to develop each manuscript
- sets timetable/priorities of manuscript development
- monitors progress of manuscript
- reassigns authorship when necessary
- gives final approval to completed manuscripts

GUIDELINES FOR REPORTING CLINICAL TRIALS

- Background
- Objectives
- Research Methods
- Results
- Discussion and Conclusions

BACKGROUND AND OBJECTIVES

- Background
  - Brief summary of principal findings of all relevant prior studies, leading to explanation as to why present study was done.
- Objectives
  - goals of study and specific hypotheses

RESEARCH METHODS

- Basic design
  - completely randomized, randomized block, cross-over, repeated measures, etc.
- Study population
  - inclusion and exclusion criteria
- Type of control group

RESEARCH METHODS

- Identification of all treatment groups. Specific methods used to administer treatments.
- Informed consent procedures
- Method of stratification and randomization
- Method of blinding

RESEARCH METHODS

- Details about measurements
  - what was measured, how, when, expected accuracy and precision.
- Identification of factors, factor levels and response variables
- Duration of study, frequency of visits
- Monitoring Procedures

RESEARCH METHODS

- Statistical methods used
  - One-sided or two-sided test?
  - Assumptions underlying tests
    - e.g. normality, proportional hazards
  - If the methods used are uncommon, may want to describe them in more detail in appendix.
  - alpha- level for statistical significance
- data quality assurance methods

STATISTICAL METHODS

- T-test
  - one-sample?
  - two-sample?
  - paired?
- Chi-square test
  - test of association?
  - goodness of fit?
  - many others possible

STATISTICAL METHODS

- Analysis of variance (ANOVA)
  - one-way, two-way, etc?
  - interaction tested?
- Regression
  - Type
    - multiple linear
    - logistic
    - Cox
- Variable selection method
  - stepwise, backward, forward, all subsets?

RESULTS

- Comparability of treatment groups
  - demographic variables
  - prognostic variables
- Efficacy results
- Safety results
  - adverse reactions
  - incidence of side effects

RESULTS

- Enumeration of patients who failed to complete study and reasons
  - withdrawals, drop-outs, losses to follow-up, code breaks
- Tests of assumptions underlying statistical procedures

RESULTS
(statistical reporting)

- always give exact p-value
- with each p-value, you should state what hypothesis is being tested (e.g. r=.53, p=.002 for H0:rho=0
- presenting computed test statistic is optional, as long as test used is accurately described
- ANOVA - summary table is helpful

RESULTS
(statistical reporting)

- Regression - include fitted model, statistical test of parameters, r2 value, plot of data and fitted regression equation
- prefer tables to graphs
- a graph can draw emphasis to an important result
- when presenting means, must present measure of variability

  (e.g. mean heart rate = 72 (s.d. = 12)

DISCUSSIONS AND CONCLUSIONS

- relate findings of present study to those of prior studies discussed in background
- if you are aware of any potential biases in sample, report them and tell how they might affect inferences
  - many VA studies include only males

DISCUSSIONS AND CONCLUSIONS

- do not draw any conclusions that are not substantiated by the data and statistical analyses
- the alpha error for planned comparisons is usually smaller than the alpha for comparisons done after looking at the data

DISCUSSIONS AND CONCLUSIONS

- Beware of numerous tests done on the same data. One in 20 will be statistically significant by chance alone.

DISCUSSIONS AND CONCLUSIONS

- Be careful in reaching conclusions based on results of study with small sample size. If a statistical test fails to reject a null hypothesis, you cannot necessarily assume that the treatments are equivalent. The probability of a Type II error must be computed and be acceptably small before the conclusion is valid.

GRAPHS

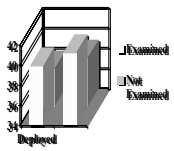
- Graphs should be fully self-explanatory. Title should include information on:
  - who or what the subjects of experiment are
  - what observations are abstracted from the subjects
  - what restrictions of time and place apply
- Vertical and horizontal axes should be clearly labeled and units should be identified.

GRAPHS

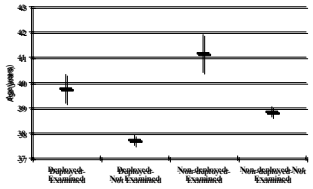
- Keep it simple. Instead of presenting many curves in one graph, you might have a series of smaller graphs each presenting one curve.
- Use direct-labeling rather than legends where possible.
- Beware of capabilities of presentation software which do not provide additional information about the data or distort the nature of the data (e.g. 3-d effects.)

Figure 7 Age
(Examined vs. Not Examined)

Bad



Good



TABLES

- Tables should be fully self-explanatory. Should stand by themselves with accurate row and column headings.
- Units should be stated for each numerical variable.
- The function of ruling is to provide clarity of interpretation. Do not overuse. Use spacing.
- Do not try to include too much information in a single table.

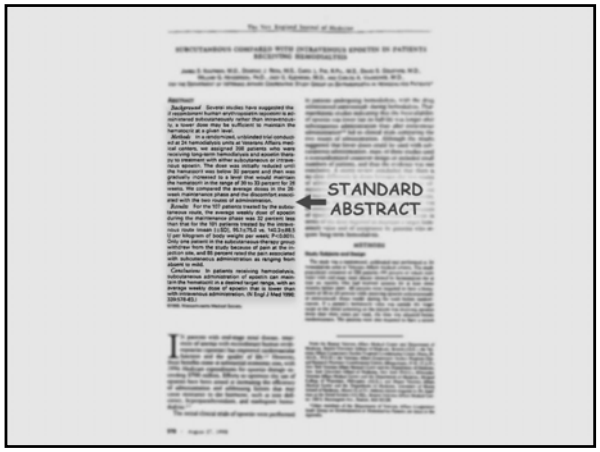
TABLES

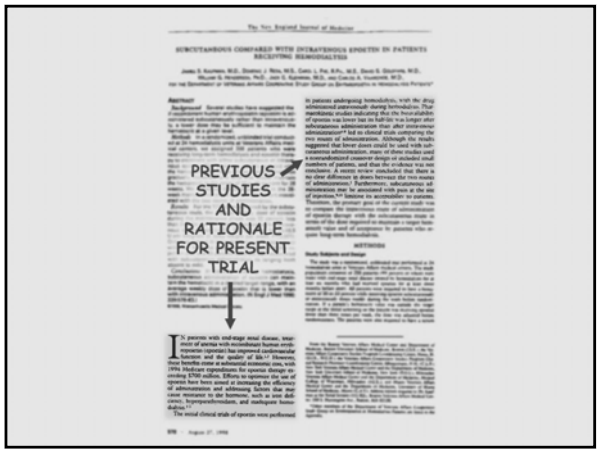
- Numerical entries of zero should be explicitly written as zero rather than indicated by a dash or dotted line (there should be reserved for missing or illogical data.
- A numerical entry should not begin with a decimal point. Use a leading zero.
- Numbers indicating values of the same characteristic should be reported to the same number of decimal places.

CONSORT

The New England Journal of Medicine

SUBCUTANEOUS COMPARED WITH INTRAVENOUS EPOETIN IN PATIENTS RECEIVING HEMODIALYSIS

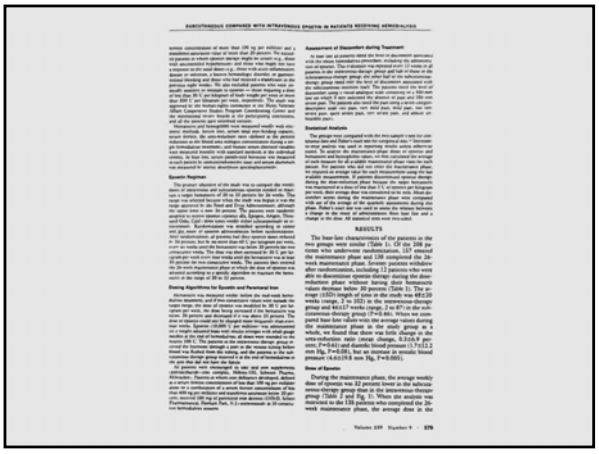

STANDARD
ABSTRACT


PREVIOUS
STUDIES
AND
RATIONALE
FOR PRESENT
TRIAL


PRIMARY
OBJECTIVE

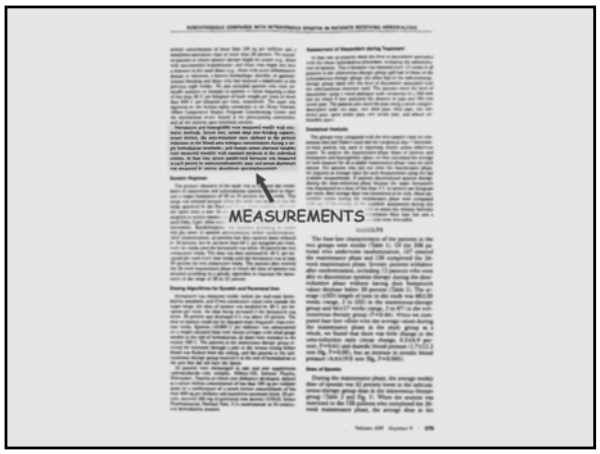

BASIC
DESIGN


PATIENT
POPULATION




EXCLUSION
CRITERIA


IRB
APPROVAL

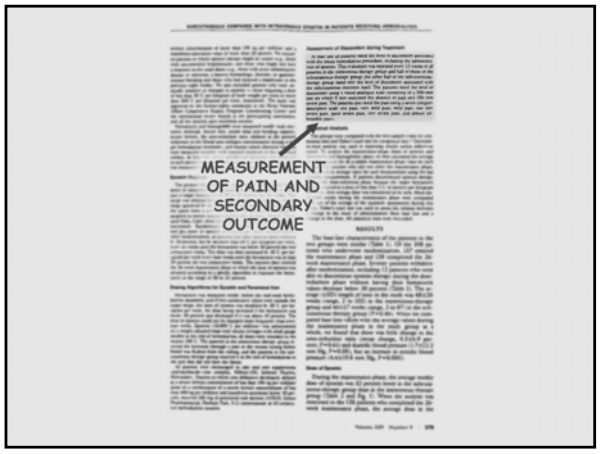

MEASUREMENTS


MORE DETAIL ABOUT
PRIMARY OBJECTIVE

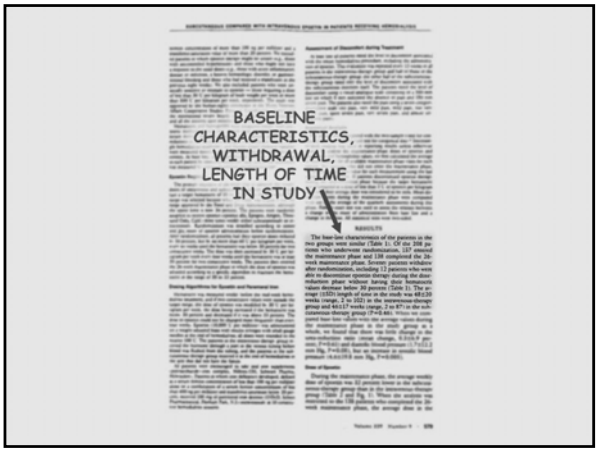

RANDOMIZATION &
STRATIFICATION


TREATMENT
REGIMEN


MORE DETAIL
ABOUT TREATMENT


MEASUREMENT
OF PAIN AND
SECONDARY
OUTCOME


STATISTICS TEST,
ITT, CALCULATIONS,
2-SIDED,
POWER α - LEVEL


BASELINE CHARACTERISTICS, WITHDRAWAL, LENGTH OF TIME IN STUDY

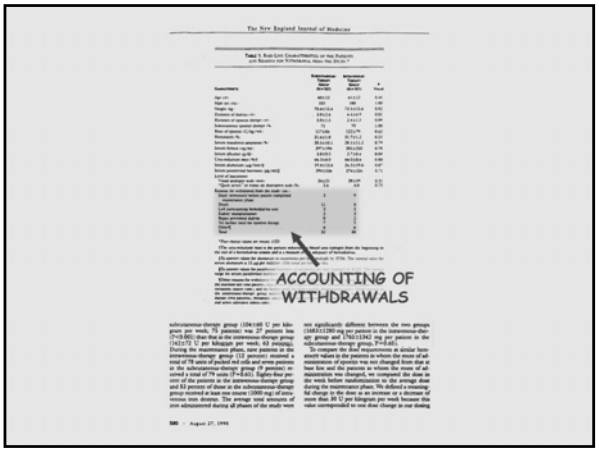

PRIMARY OUTCOME (ITT)

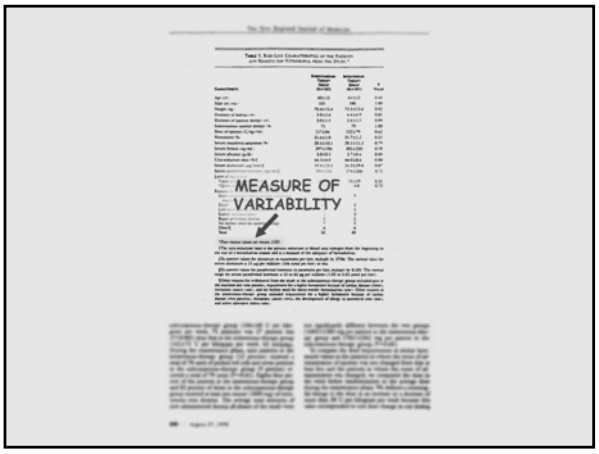

OUTCOME IN AS TREATED GROUP

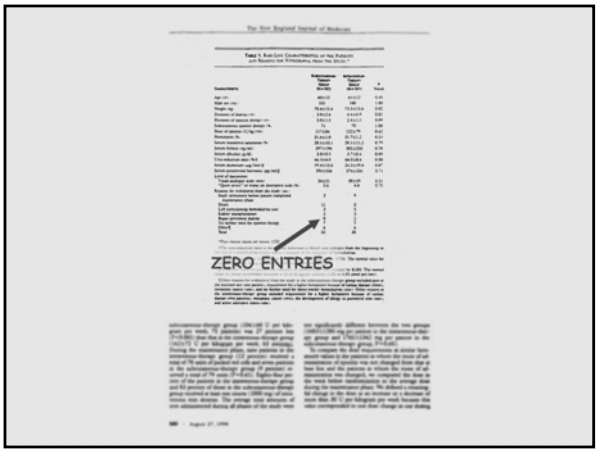
The New England Journal of Medicine

TABLE STANDS BY ITSELF

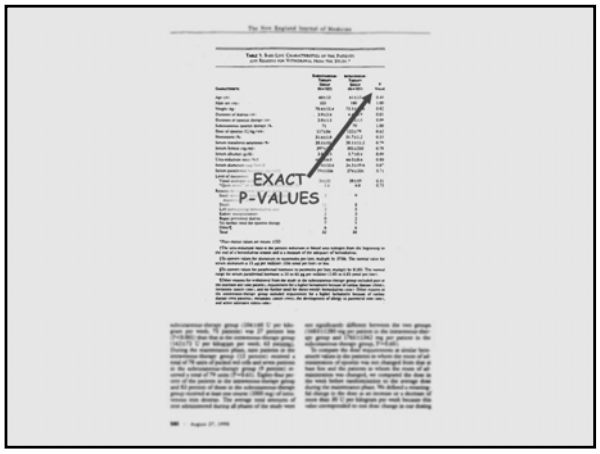
BASELINE COMPARISONS


ACCOUNTING OF
WITHDRAWALS


MEASURE OF
VARIABILITY


ZERO ENTRIES

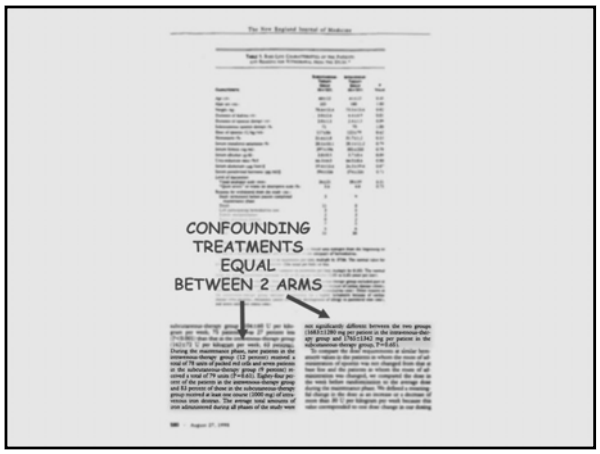

LEADING ZERO


EXACT
P-VALUES

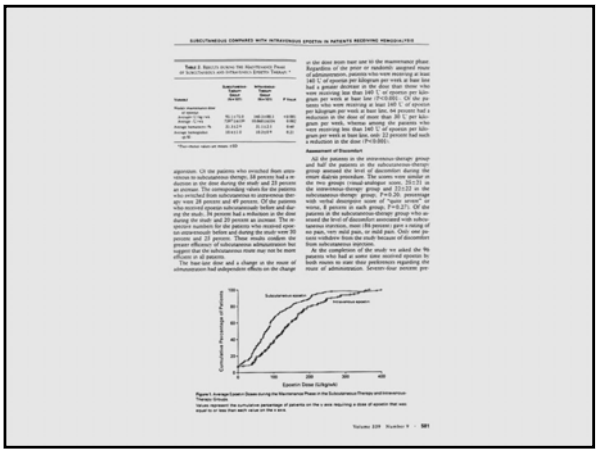

UNITS

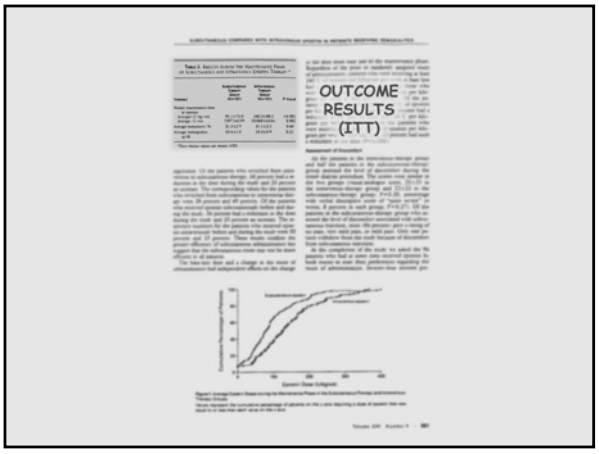

SAMPLE SIZES

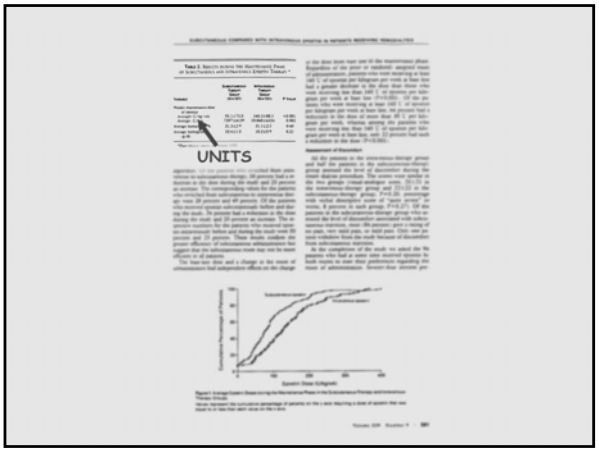

OUTCOME IN AS TREATED GROUPS


CONFOUNDING TREATMENTS EQUAL BETWEEN 2 ARMS


SUBGROUP
ANALYSES
COMPARISONS
WITHIN
PATIENTS




OUTCOME
RESULTS
(ITT)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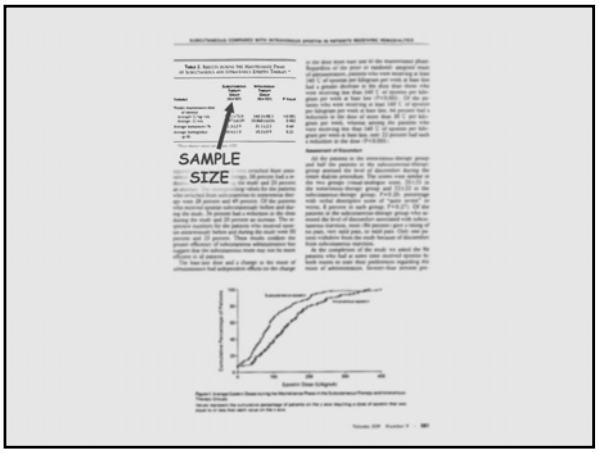
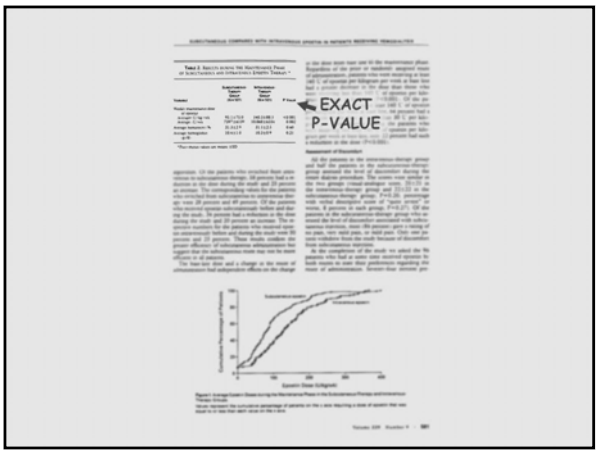

SAMPLE
SIZE


EXACT
P-VALUE

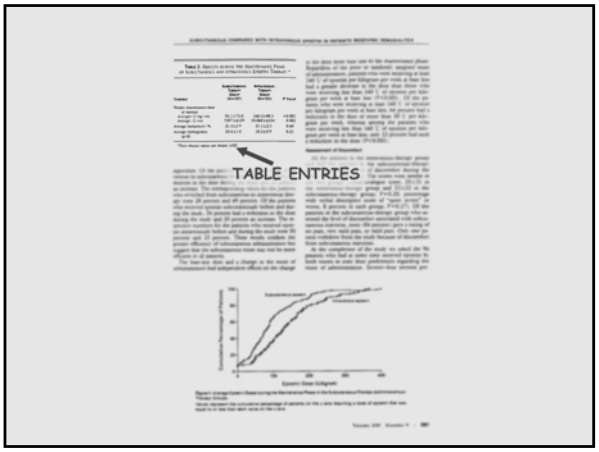
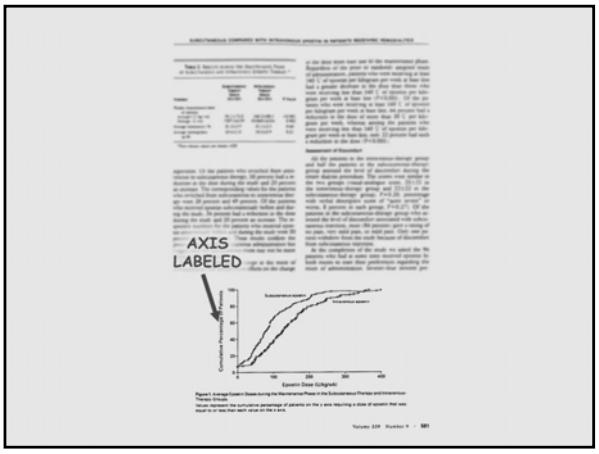
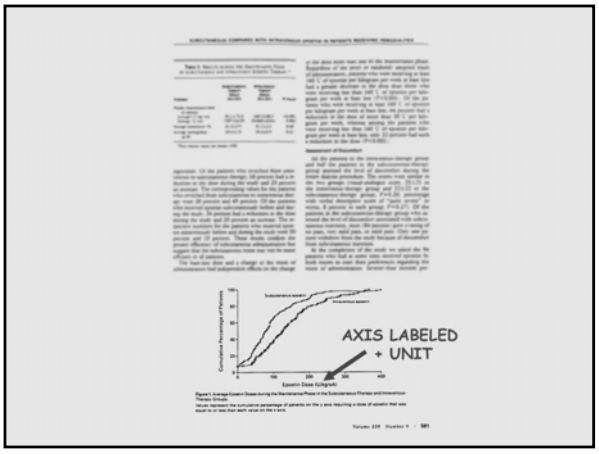
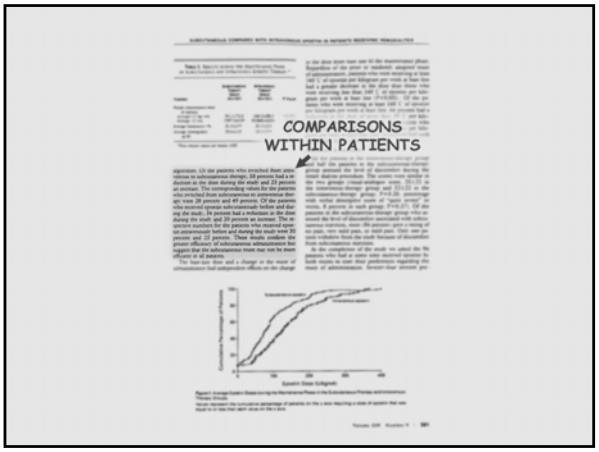
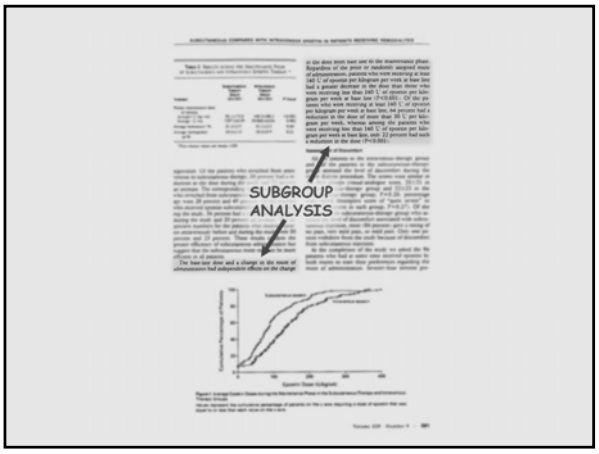


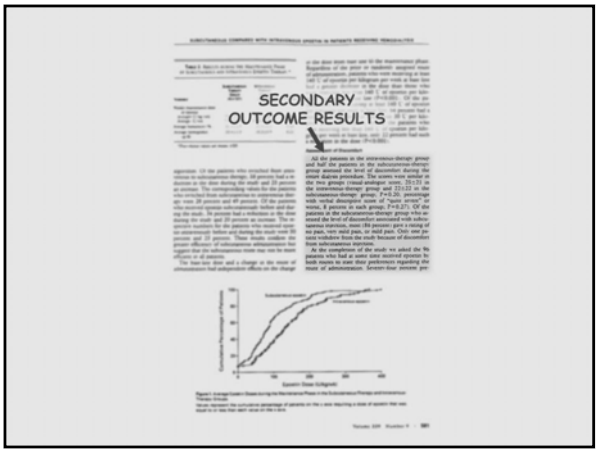
TABLE ENTRIES

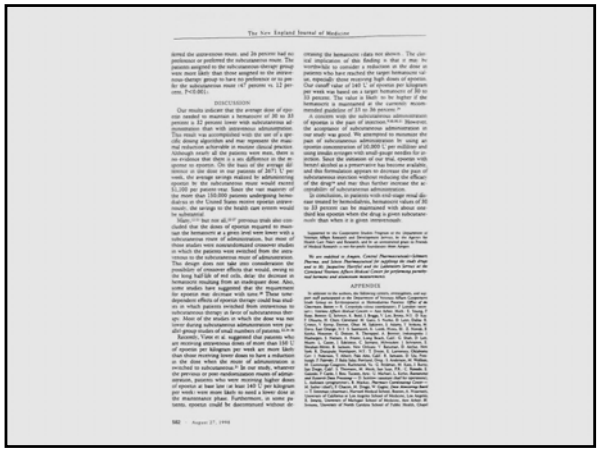

AXIS LABELED


AXIS LABELED
+ UNIT


COMPARISONS
WITHIN PATIENTS

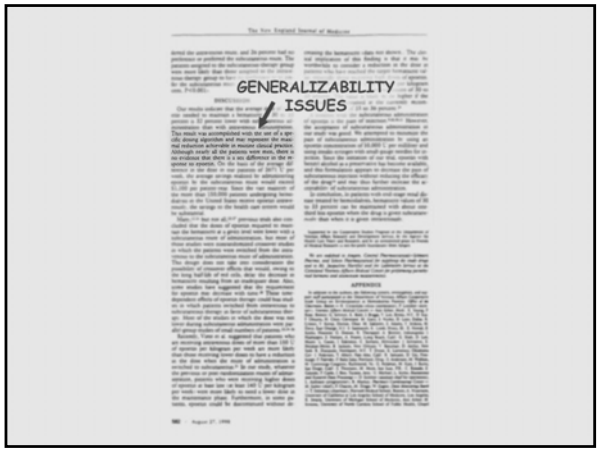

SUBGROUP
ANALYSIS


SECONDARY
OUTCOME RESULTS

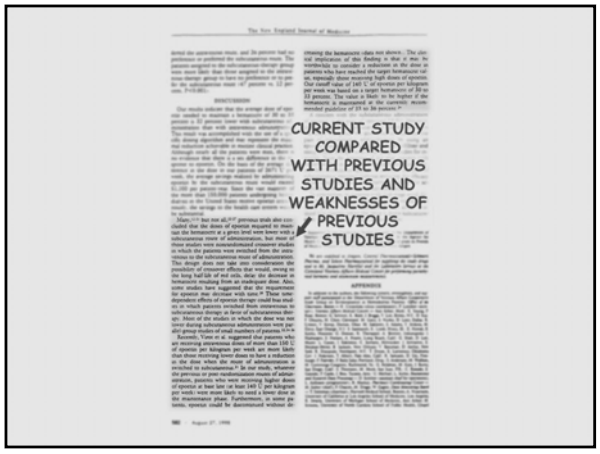



SECONDARY
OUTCOME


REINTERATE
CONCLUSION


GENERALIZABILITY ISSUES

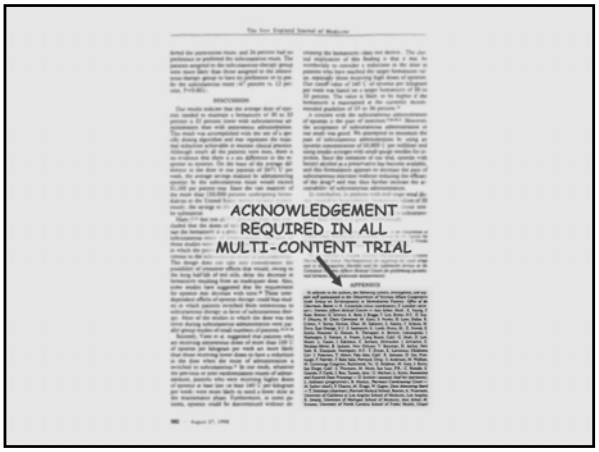

ECONOMIC IMPACT


CURRENT STUDY COMPARED WITH PREVIOUS STUDIES AND WEAKNESSES OF PREVIOUS STUDIES


DISCUSSION OF
SECONDARY
OUTCOMES


CONCLUSION


FUNDING SOURCE



Tips To Getting Your Research Published -What They Don't Want You To Know

- Include a co-author from Harvard, Yale, Stanford or Duke
  - Even if you don't personally know them
- P>.05?
  - Don't even bother
  - Consider deleting "unusual" cases
- Money talks but make sure it can be heard
  - Don't insult the editor, make sure the "donation" is large enough
  - It is acceptable to include a signed blank check as Appendix A.

Tips To Getting Your Research Published -What They Don't Want You To Know

- Include one of the following as a treatment arm
  - Magnets
  - Sham surgery
  - Gingko Biloba
- Use a random title generator
  - A sexy title will get you in the door even if it bears absolutely no relationship to the research

Example

- A comparison of ____ with ____ for the treatment of ____ : _____
- Treatment A
  1. Magnets
  2. Jointritis
  3. Gene Therapy
- Treatment B
  1. Sham Surgery
  2. Gingko Biloba
  3. Prayer

Example

- Diseases
  1. Chronic Fatigue Syndrome
  2. Male Pattern Baldness
  3. Mad Cow Disease
- Closer
  1. A cost-effectiveness analysis
  2. Results of the Physician's Health Study
  3. A meta-analysis